REMARKS

Claims 1, 4-5, 7-9, 11-16 and 18-30 are pending. Claims 18-28 have been withdrawn from consideration; claims 2, 3, 6, 10, and 17 have been canceled without prejudice or disclaimer; and claims 1, 4-5, 7-9, 11-16, and 29-30 are currently under active examination.

Independent claims 1 and 30 have been amended to specify that carrier protein is covalently coupled to the polysaccharide at "de-O-acetylation sites." Support for the amendment can be found, e.g., at paragraphs 0066-0068, describing coupling carrier protein to the polysaccharide by reductive amination at activated carbonyl groups formed at de-O-acetylation sites. Furthermore, the specification teaches that any free primary amines, resulting from de-N-acetylation, can be re-N-acetylated. See, e.g., paragraph 0039. This plainly teaches one of skill in the art that in such embodiments no de-N-acetylation sites remain available for protein conjugation, so that carrier protein is necessarily covalently coupled to the polysaccharide "at the de-O-acetylation sites." Finally, claim 13 has been amended to correct a dependency and the spelling of "meningitidis" has been corrected in a number of claims. Accordingly, the amendments raise no new matter issues.

Withdrawn Rejections

Applicants acknowledge with thanks withdrawal of previous rejection of claims 1-2, 6-10, and 12-17 under 35 U.S.C. 102(b). Applicants also acknowledge with thanks withdrawal of previous rejection of claims 1-17 under 35 U.S.C. 103(a).

New Rejections under 35 U.S.C. 103(a)

The Office has rejected claims 1, 4-5, 7-9, 11-16, and 29-30 under 35 U.S.C. 103(a) as allegedly obvious in view of Costantino WO 03/007985, in view of Porro U.S. 2006/0165730, and further in view of Michon et al WO 00/10599. Action at pages 2-6. The Office alleges that Costantino teaches a polysaccharide fragment from O-acetyl positive group Y of N. meningitis, having a MW less than about 150 kDa, where the saccharide is conjugated to a carrier protein, but acknowledges that Costantino does not teach that the polysaccharide has been O-deacetylated by at least 80% nor that it is completely N-acetylated. Action at pages 3-4. The Office points to Porro as teaching the degree of de-O-acetylation; and to Michon as teaching complete N-acetylation, alleging that it would have been *prima facie* obvious to modify Costantino's polysaccharide by the de-O-acetylation taught in Porrro and by the complete N-acetylation allegedly taught in Michon. Action at pages 4-6. Applicants respectfully traverse as none of the cited references teach a completely N-acetylated polysaccharide fragment and, moreover, none provide motivation to completely N-acetylate a polysaccharide fragment that is covalently coupled to carrier protein at de-O-acetylation sites, as currently required by the pending claims.

1. No reference teaches a completely N-acetylated Polysaccharide

Michon teaches a method of preparing an immunogenic polysaccharide-protein conjugate by removing N-acetyl groups from the polysaccharide and replacing them with N-acryloyl groups, which are in turn coupled to protein. See Michon, p. 4, lines 20-22. As noted in our previous response, however, Michon fails to teach complete

N-acetylation as Michon explicitly states that *only a portion* of the de-N-acetylated groups are converted into N-acryloyl groups for coupling to protein:

> "[a] percentage of the N-acetyl groups removed by hydrolysis from the polysaccharide are replaced by N-acryloyl groups, which in turn, are directly coupled to protein to form the conjugate of the present invention." Michon, p. 4, lines 20-22.

As some de-N-acetylated groups remain, it is evident that the polysaccharides of Michon are not "completely N-acetylated" as required by the claims.

Neither Porro nor Costantino can correct this deficiency. Porro and Costantino both teach hydrolysis of polysaccharides that are eventually coupled to carrier protein via reductive amination, but neither anywhere suggests or hints at re-N-acetylation. Hydrolysis of the polysaccharide, however, can generate free primary amines, which remain as de-N-acetylation sites if not re-N-acetylated. See paragraph 0039 of the instant specification. Porro teaches de-O-acetylation by hydrolysis, followed by activation at the de-O-acetylated sites, which are then coupled using a spacer to activated carrier protein via reductive amination. See paragraphs 0025-0045. Costantino teaches hydrolysis of the polysaccharide and also eventual conjugation a carrier protein via reductive amination. See pages 15-18. Nonetheless, neither reference recognizes, much less addresses the problem of de-N-acetylation to generate free primary amines, as taught in the instant specification. Accordingly, neither reference teaches or suggests any re-N-acetylation of the resulting free primary amines, necessarily leading to conjugates where the polysaccharide fragment is not "completely N-acetylated", as required by the claims. As neither Porro, nor Costantino, nor Michon can provide the required element

of complete N-acetylation, there can be no *prima facie* case of obviousness based on the cited references.

For at least this reason, Applicants respectfully and earnestly request reconsideration and withdrawal of the rejections directed at claims 1, 4-5, 7-9, 11-16, and 29-30.

2. There is no motivation to re-N-acetylate the polysaccharide

Applicants respectfully submit that the cited references also fail to provide any motivation to re-N-acetylate a polysaccharide that is covalently coupled to carrier protein at de-O-acetylation sites, as required by the currently amended claims, rather than at de-N-acetylation sites, as in Michon. As noted above, Michon teaches converting polysaccharide N-acetyl groups into N-acryloyl groups, which in turn are coupled to protein to form conjugates. See Michon, p. 4, lines 20-22. Thus in Michon, the carrier protein is coupled at de-N-acetylation sites rather than de-O-acetylation sites, and N-acryloylation is carried out to form the polysaccharide-protein conjugates, rather than relying on reductive amination.

In contrast, as noted above, Porro and Costantino teach hydrolysis of the polysaccharide and conjugation to carrier protein via reductive amination. Unlike the instant specification, however, neither reference recognizes, much less addresses, the problem of de-N-acetylation and generation of free primary amines. Without any understanding of this potential issue, there would be no reason or motivation to carry out re-N-acetylation to arrive at the completely N-acetylated polysaccharide fragments of the instant claims.

Michon does nothing to provide the missing motivation. Michon's N-acryloylation is carried out in a completely different context from the conjugation reactions of Porro and Costantino. Rather than de-O-acetylation and reductive amination, Michon intentionally de-N-acetylates the polysaccharide to then N-acryloylates to couple the carrier protein at the de-N-acetylation sites. Applicants respectfully submit that one of skill in the art thus would have no motivation to modify the polysaccharides of Costantino or Porro by the N-acryloylation taught in Michon, as Costantino and Porro use very different coupling reactions to form distinctly different conjugate products. Without any motivation to modify Costantino's or Porro's polysaccharides with Michon's N-acryloylation, Applicants respectfully submit that there can be no *prima facie* case of obviousness in view of the cited references.

In sum, we note that none of the cited references recognize nor address the importance of complete re-N-acetylation following de-O-acetylation of meningococcal polysaccharides, in the context of preparing immunogenic conjugates, and as taught by the instant inventors. The art failed to recognize that any remaining free primary amines could compromise the integrity of the immunogenic conjugate, e.g., by zwitter ion formation or oxidative cleavage of the polysaccharide component. Indeed, current studies indicate that the group Y meningococcal polysaccharide epitope is a relatively large structure, composed of 5 to 6 repeating sugar units. Moore et al. (2007) Clinical and Vaccine Immunology 14(10): 1311-1317. As breakage at any remaining de-N-acetylated sites would destroy this large epitope structure, complete N-acetylation is particularly important for retaining antigenicity in group Y meningococcal vaccines.

For at least the above reason, Applicants respectfully and earnestly request re-consideration and withdrawal of the non-obviousness rejections directed at claims 1, 4-5, 7-9, 11-16, and 29-30.

CONCLUSION

In view of the foregoing remarks and amendments, Applicants respectfully submit that claims 1, 4-5, 7-9, 11-16, and 29-30, as currently amended, are non-obvious over all cited references and earnestly and respectfully request timely allowance of same. In the event that the Examiner believes that issues exist that can be resolved by telephone conference, or that any formalities can be corrected by an Examiner's Amendment, a telephone call to the undersigned at (212) 827-4318 is respectfully requested.

Respectfully submitted,
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